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10/18/10

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(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Catherine Castan et al.

Application No.: 10/510,643

Confirmation No.: 1869

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Art Unit: 1615

For: ORAL PHARMACEUTICAL FORMULATION
IN THE FORM OF AN AQUEOUS
SUSPENSION OF MICROCAPSULES FOR
THE MODIFIED RELEASE OF ACTIVE
PRINCIPLE(S)

Examiner: C. E. Helm

DECLARATION OF PHILIPPE CAISSE

1. My name is Philippe CAISSE.
2. I have been an employee of Flamel Technologies since 1991.
3. My position at Flamel Technologies is senior scientist at the Oral Forms Research Department.
4. I have a MSc in Polymer Science & Technology from Loughborough University.
5. I have worked in the area of pharmaceutical compositions for 19 years.
6. I consider myself to be one of skill in the art of oral pharmaceutical compositions for delayed and controlled release of active principles.
7. I supervised Noelle Villard and Jean-Luc Terrance who prepared or tested the below two different Compositions and four suspensions.
8. To the best of my knowledge, the information below is an accurate description of how these Compositions and suspensions were prepared, and their release profiles measured.
9. Composition 1 is a commercially available capsule of the active principle **ibuprofen**: Nureflex[®] LP 300mg (Reckitt Benckiser Healthcare France - Marketing Authorization No. AMM 336 863.4). It contains coated microparticles that provide sustained release of ibuprofen for the treatment of rheumatism pain. The composition disclosed in the

Vidal¹ on-line formulary indicates that the product is composed of sugar spheres, Eudragit E100, povidone, Eudragit RL100, colloidal silicon dioxide, talc and gelatin. The sugar spheres are the neutral particles supporting the drug layer and the coating, gelatin is the material of the capsule, talc and colloidal silicon dioxide are glidants used admixed with the coated particles. Therefore, the coating composition of Nureflex LP 300mg contains Eudragit E100, Eudragit RL100 and maybe povidone. Eudragit E100 is a polymer soluble at pH below 5 whose chemical name is poly(butyl methacrylate, (2-dimethylaminoethyl) methacrylate, methylmethacrylate) 1:2:1.

Eudragit RL100 is an insoluble polymer, whose chemical name is poly(ethyl acrylate, methylmethacrylate, trimethylammonioethyl methacrylate chloride) 1:2:0.2.

10. Composition 2 was formed of the active ingredient **carvedilol phosphate**, coated with a blend of 60% of polymer Eudragit L100-55 ("methacrylic acid copolymer, Type C" USP/NF) and 40% of insoluble Lubritab (hydrogenated cottonseed oil).

11. Figures 1 to 4 below demonstrate that these two compositions failed to preserve their release profile after a few days of storage at ambient temperature in a liquid suspension vehicle which was initially saturated, or not, with the active principle. The preparation of Composition 2 and the suspensions made from Composition 1 and 2 are detailed hereafter.

12. Composition 1

a. A suspension of Composition 1 was prepared as follows:

i. The content of a capsule of Nureflex[®] LP 300mg corresponding to 300 mg ibuprofen was added to 15ml of a 2.0 g/l solution of xanthane (Xantural 75[®]) in pH 4.5 medium (monobasic potassium phosphate buffer 0.05M).

b. A saturated suspension of Composition 1 was prepared as follows:

i. 30 mg of ibuprofen were added to 15ml of a 2.0 g/l solution of xanthane (Xantural 75[®]) in pH 4.5 medium (monobasic potassium phosphate buffer 0.05M). The solubility of ibuprofen at pH 4.5 is about 0.2g/l. Hence the quantity of added ibuprofen is tenfold the solubility. The content of a capsule of Nureflex LP 300mg corresponding to 300 mg ibuprofen was then added to this saturated suspension.

c. Composition 1 and the corresponding suspensions were tested as follows:

¹<http://asp.evidal.net> accessed on 7 July 2010

- i. The microparticles and the two suspensions of microparticles, stored several days at room temperature, were tested in a USP type II dissolution apparatus in 900 ml of pH 6.8 medium (monobasic potassium phosphate buffer 0.05M) maintained at 37.0 ± 0.5 °C , agitated by a rotating paddle at 100 rpm.
- d. The release profiles of Composition 1 microparticles and of the corresponding suspension stored 9 days at room temperature are shown in Figure 1. The value obtained for the similarity factor f_2 was:

$$f_2 = 38$$

Hence, the curves are not similar, showing the lack of stability of the release kinetics.

- e. The release profiles of Composition 1 saturated suspension, initially and after storage 7 days at room temperature are shown in Figure 2. The value obtained for the similarity factor f_2 was:

$$f_2 = 48$$

The curves are not similar, showing the lack of stability of the release kinetics.

- f. Whatever the manufacturing process, with pre-saturation of the liquid with the active principle or not, the sustained release coating of Nureflex[®] LP 300mg does not keep a constant permeability upon storage in a liquid suspension.

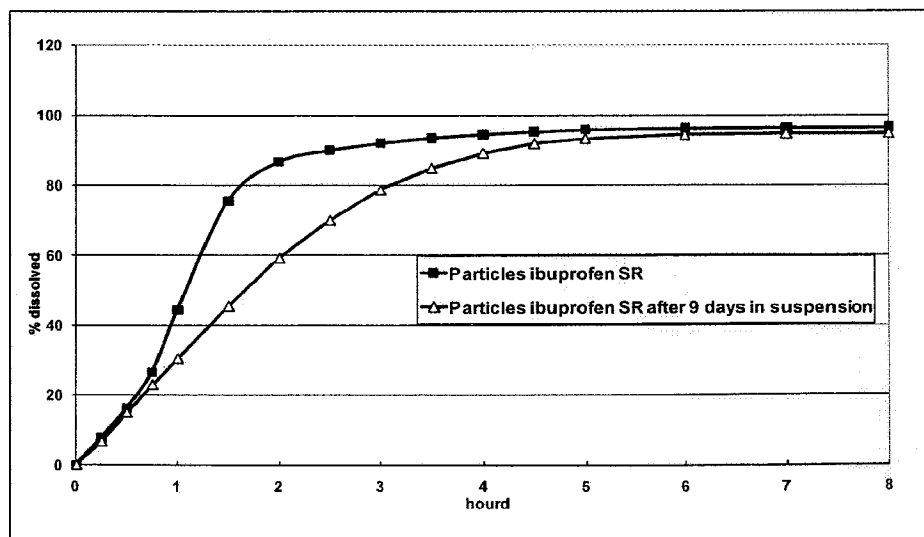


Figure 1

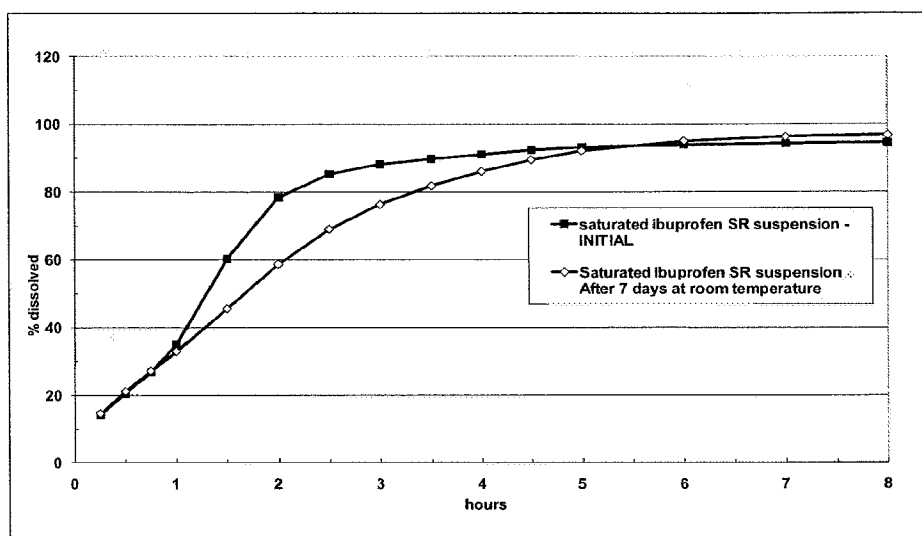


Figure 2

13. Composition 2

a. Composition 2 was prepared as follows:

- i. A suspension composed of 170.0 g polyvinylpyrrolidone; 297.5 g cross-linked polyvinylpyrrolidone; 42.5 g polyoxyl 40 hydrogenated castor oil and 340.0 g carvedilol phosphate in 1983.33 g water was sprayed onto 850.0 g cellulose spheres in a fluid bed spray coater apparatus Glatt® GPCG1.1 to obtain microgranules. Microgranules with size comprised between 200 and 500 μm were retained.
- ii. A solution composed of 86.40 g of methacrylic acid copolymer; 57.60 g of hydrogenated cottonseed oil dissolved in 884.57 g of isopropyl alcohol was sprayed entirely onto 456.0 g of the above prepared microgranules in a fluid bed spray coater apparatus Glatt® GPCG1.1

b. A suspension of Composition 2 was prepared as follows:

- i. A quantity of carvedilol phosphate sustained release microparticles corresponding to 80 mg of carvedilol phosphate was added to 10 ml of a 2.0 g/l solution of xanthane (Xantural 75®) in pH 4.5 medium (monobasic potassium phosphate buffer 0.05M).

c. A saturated suspension of Composition 2 was prepared as follows:

- i. A quantity of carvedilol phosphate sustained release microparticles corresponding to 80 mg of carvedilol phosphate was added to 10 ml of a 2.0 g/l solution of xanthane (Xantural 75®) in pH 4.5 medium (monobasic potassium phosphate buffer 0.05M) containing 30mg of carvedilol

phosphate to saturate initially the suspension (solubility of carvedilol phosphate is <0.5 mg/ml at pH4.5).

- d. The suspensions of Composition 2 were tested as follows:
- The suspensions were tested in a USP type II dissolution apparatus in 900 ml of HCl 0.1N kept at 37.0 ± 0.5 °C and stirred by a rotating paddle at 100 rpm.
- e. The release profiles of Composition 2 and its corresponding unsaturated suspension after storage at room temperature are shown in Figure 3. The two curves are not similar with a calculated f_2 value of:

$$f_2 = 24$$

and thus demonstrate the instability of the particle release kinetics inside the liquid suspension.

- f. The release profiles of Composition 2 saturated suspension, initially and after storage at room temperature, are shown in Figure 4. The two curves are not similar with a calculated f_2 value of:

$$f_2 = 48$$

showing evolution of particle release kinetics in the liquid medium.

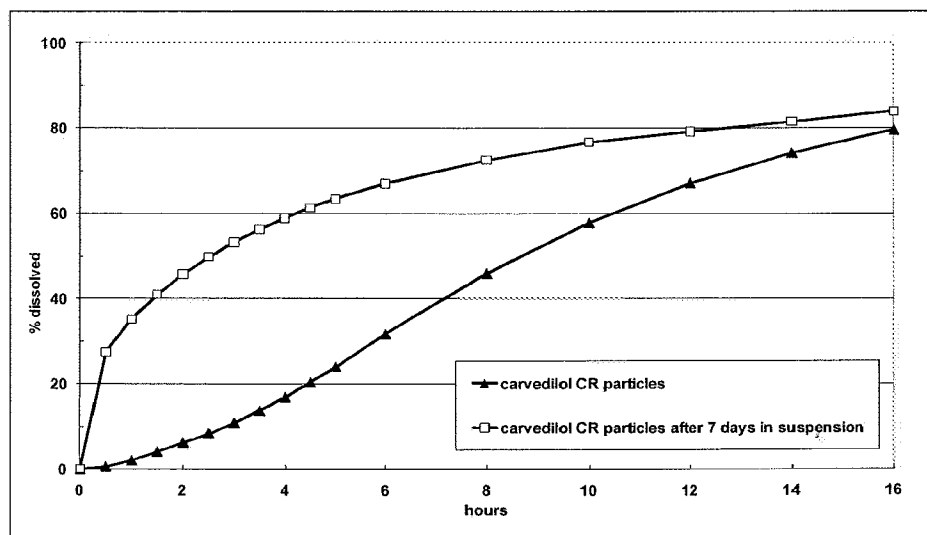


Figure 3

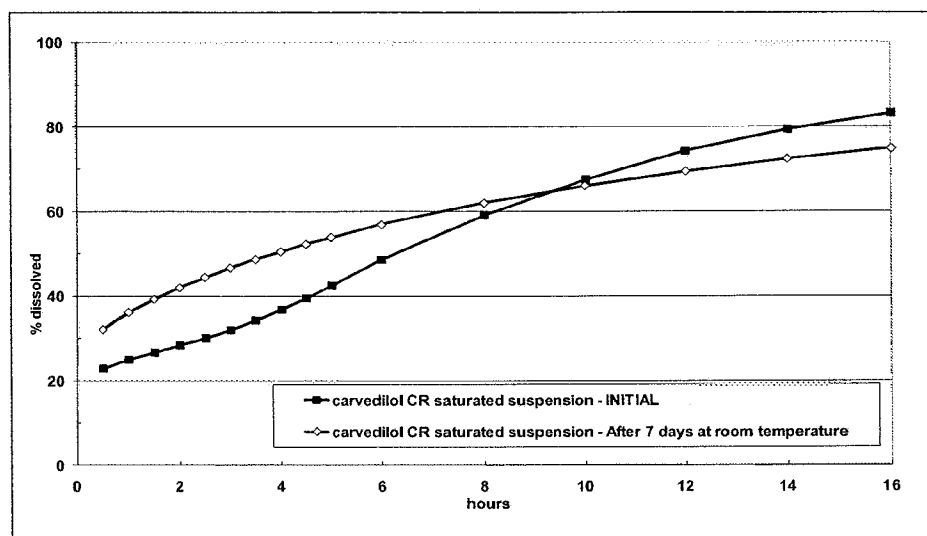


Figure 4

14. I declare that all statements made of my own knowledge are true, and all statements made on information and belief are believed to be true. I make this declaration with the understanding that willful false statements and the like are punishable by fine or imprisonment, or both (18 U.S.C. 1001) and may jeopardize the validity of the patent application.


Philippe CAISSE

October 15, 2010